REMARKS

Claims 1-3 and 12 are pending. Claims 4-11 and 13-90 have been canceled as being drawn to a non-elected invention. The claims were subject to a restriction requirement, and Applicants elected Group I (claims 1-12). The claims were also subject to a species election, and Applicants elected myocardial tissue as the elected species for tissue type and stromal derived factor-1 (SDF-1) as the elected species for a therapeutic molecule.

The claims have been amended to address the Examiner's concerns. No new matter has been added by this amendment.

37 U.S.C. § 112

Claims 1-3 and 12 were rejected for overbreadth and lack of enablement, because the claims:

> while being enabling for regenerating myocardial tissue by local administration of isolated adult mesenchymal cells expressing an exogenous nucleic acid encoding an akt gene, and further encoding a growth factor gene; does not reasonably provide enablement for regenerating myocardial tissue by administering, via any route, isolated adult mesenchymal stem cells expressing an exogenous nucleic acid encoding an akt gene, and further encoding a SDF-1 gene. (paragraph spanning 2-3 of Office action)

To expedite allowance, claim 1 has been amended to require local administration, and new claim 91 further requires local administration to a damaged portion of the heart.

With regard to SDF-1, the Examiner further stated:

> Instantly elected species of a growth factor is SDF-1. Although the specification prophetically teach delivering such among a list of "injury-associated polypeptides" (Specification, page 9, line 7), neither the art of record nor the specification teaches how SDF-1 is associated with cardiac injury, and what kind of effect SDF-1 may assert on cardiac cells, and thus fails to provide sufficient guidance to support the full scope of the claims.

This rejection is traversed.

New claims 92-95 further require that the Akt-mesenchymal stem cell contain an exogenous nucleic acid encoding a growth factor or injury-associated molecule such as SDF-1.

Contrary to the Examiner's statement above, the specification provides teaching as to how SDF-1 is associated with cardiac injury. Specifically, Applicants teach that certain injury-

associated polypeptides, e.g., SDF-1 participates in cardiac repair by influencing homing and migration (page 42, lines 7-19, of the specification; Table 3 (page 46 of the specification); and Figs. 19A-B. This discovery, teaching, and indeed forward thinking, by Applicants provide the foundation for the claimed methods that require augmentation of production of SDF-1 by stem cells by introduction of exogenous SDF-1-encoding sequences. Akt-mesenchymal stem cells further comprising SDF-1-encoding nucleic acids provide a reliable, apoptosis-resistant, long-lived stem cell population that localizes to injured tissue - a useful therapeutic tool for tissue regeneration. In fact, subsequent publications (e.g., Zhang et al, 2007, FASEB J., epub May 11, 2007; copy attached as Appendix A) citing Applicant's work confirm that SDF-1 plays a role in homing of stem cells and progenitor cells to the myocardium as well as trophic support of cardiac myocytes after myocardial infarction leading to enhancement of the regenerative repair process. Thus, not only is adequate guidance provided in the specification as filed to support the full scope of the amended claims, subsequent reports by independent researchers regarding SDF-1 confirms and validates the methods disclosed and claimed. Applicants therefore request withdrawal of this rejection.

35 U.S.C. § 103

Claims 1-3 were rejected for obviousness over Matsui et al. in view of Greenberger et al. (USPN 5,993,801; "the '801 patent") and Fukuda et al. On page 6 of the Office Action, the Examiner states:

> it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by Matsui et al, with that of Greenberger and Fukuda et al, by administering mesenchymal stem cells expressing an exogenous Akt gene in place of the adenoviral vector as taught by Matsui et al with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because not only MSC is a well know transgene carrier but also have the potential to directly repair/regenerating cardiomyocytes.

This rejection is traversed. Matsui et al. describe administration of an adenoviral vector encoding Akt in an area subjected to ischemia and observed a "powerful cardioprotective effect" using a gene therapy approach. Matsui et al. is limited to administration of a nucleic acid and does not describe or suggest cell therapy - a completely different approach. One practicing in the art of gene therapy would not necessarily be motivated or inclined to look to cells as a gene

delivery means despite the availability and awareness of host cells that can serve to act as a "transgene carrier". In fact, almost any cell can act as a "transgene carrier". In this case, Matsui et al. reported success with their gene therapy approach. Even if their approach was deemed to be less than successful, artisans skilled in the art of gene therapy would not change their approach to administering cells by merely having knowledge of the existence of a cell "transgene carrier".

The '801 patent describes stromal cells transfected with an exogenous gene to correct a genetic deficiency, i.e., the gene to be transfected is the gene that is deficient in the subject to be treated. For example, cells are transfected with a gene encoding Factor VIII-C to treat a bleeding disorder, Hemophilia A, characterized by a deficiency of this factor. The Matsui et al. reference does not describe replacement of a deficient gene, nor do those researchers discuss alternative strategies to deliver their gene of interest. Therefore, there is no reason articulated or implicit to combine these two references. Moreover, there is no reason to believe that the effect of Akt on mature ischemic heart cells/tissue as described in Matsui would be the same or similar to the effect of Akt in immature cells such as mesenchymal stem cells as claimed.

Fukata et al. describe establishment of a cardiomyogenic cell line from mouse bone marrow stromal cells and their use for cardiovascular tissue engineering. These researchers used 5-azacytidine to immortalize the cells and screened for spontaneously beating cells. As with the '801 patent, the mere existence or awareness of this type of cell to the skilled artisan practicing gene therapy is not tantamount to a motivation to change his or her strategy of delivering a gene. As is discussed above, there is no reason to believe that Akt would have the same or similar effect on mature tissue (e.g., cardiac tissue as described by Matsui et al. compared to immature cells (e.g., bone marrow stromal cells) or a cardiomyogenic cell line. Thus, there is no support for the rationale to regenerate mesenchymally-derived tissue with MSCs transfected with an akt gene.

Even if these references did establish a *prima facie* case for obviousness, evidence of unexpected results and advantages must be considered to overcome the rejection The specification discloses recombinant Akt-mesenchymal stem cells that are genetically enhanced for increased post-transplant survival when engrafted into striated cardiac muscle that has been damaged through disease or degeneration and decreased apoptosis. Akt-mesenchymal stem cells are characterized by prolonged viability (several days) in the engrafted tissue compared to stem

cells lacking the akt sequences, which die in the peri-transplantation period, e.g., within 24 hours following transplantation (page 3, lines 8-34, of the specification; page 35, line11, to page 36, line 8, of the specification; and Figs. 11A-D, 12A-B). Intramyocardial delivery of these Akt-mesenchymal stem cells led to a remarkable reduction in infarct volume (44.8% reduction in infarct volume and 84.7% regeneration of lost myocardium; page 36, lines 9-27, of the specification; and 13A-B, 14, and 15). Such a marked increased in survival/engraftment, effect on infarct size, and normalization of cardiac function would not have been expected by the skilled artisan and represent significant advantages that overcome many of the drawbacks of previous therapeutic methods. Applicants therefore request withdrawal of this rejection.

Claim 12 was rejected for obviousness over Matsui et al. in view of the '801 patent and Fukuda et al., in further view of Palasis. Claim 12 depends from claim 1 and further requires that the mesenchymal stem cell contains exogenous nucleic acid encoding a cytokine or growth factor. Matsui et al, the '801 patent, and Fukuda et al. were discussed above. This combination of references does not render obvious Akt-modified mesenchymal stem cells, and none of the foregoing references describe or suggest a cytokine or growth factor. Palasis describes angiogenic factors and certain growth factors. However, the addition of Palasis to the earlier combination of references do not suggest methods of tissue regeneration by administering Akt-modified mesenchymal stem cells that have been further modified to encode a cytokine or growth factor.

Claim 12 was also rejected for obviousness over Matsui et al. in view of the '801 patent and Fukuda et al. in further view of Pillarisetti et al. Applicants note that the elected species for an exogenous nucleic acid encoding a "specific therapeutic molecule" is SDF-1. The Pillarisetti reference was cited for its description of SDF-1. The reference describes cloning of rat SDF-1 and expression profiles thereof; SDF-1α was found to be in induced in a coronary occlusion model of myocardial infarction while SDF-1γ remained unchanged. Adding this reference to the combination of Matsui, Fukuda, and the '801 patent also fails to provide a suggestion to administer Akt-modified mesenchymal stem cells that further comprise an exogenous SDF-1-encoding nucleic acid for tissue regeneration.

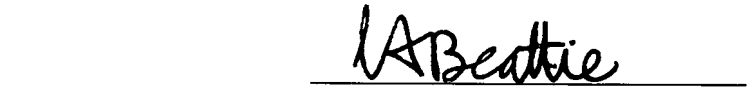
CONCLUSION

In summary, the combination of references cited by the Examiner does not suggest the claimed methods for tissue regeneration by administering adult mesenchymal stem cells that have been modified to contain an exogenous nucleic acid encoding Akt and further such a stem cell containing both Akt-encoding nucleic acids and another exogenous nucleic acid encoding a growth factor or cytokine such as SDF-1.

Applicants submit herewith a Petition for a Three-Month Extension of Time, along with the appropriate fees under 37 C.F.R. 1.17(a)(5). No additional fees are believed to be due in connection with this filing. If there are any questions, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

The Commissioner is hereby authorized to credit any overpayment or charge any deficiencies to Deposit Account No. 50-0311 (Reference No. 18989-028).

Respectfully submitted,



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